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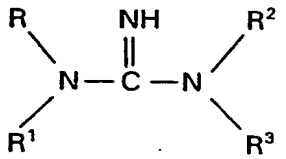
(54) Title: THERAPEUTIC SUBSTITUTED GUANIDINES

(57) Abstract

The present invention provides therapeutically useful substituted guanidines and methods of treatment and pharmaceutical compositions that utilize or comprise one or more of such guanidines.

What is claimed is:

1. A compound of the following Formula I:



I

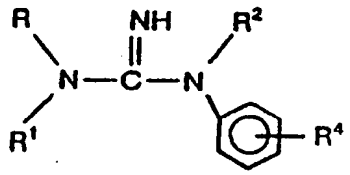
wherein R, R^1 and R^2 are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkoxy, substituted or unsubstituted thioalkyl, substituted or unsubstituted aminoalkyl, substituted or unsubstituted carbocyclic aryl having at least about 6 ring carbon atoms, substituted or unsubstituted aralkyl having at least about 6 carbon ring atoms, or a substituted or unsubstituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 ring members in each ring and from 1 to 3 hetero atoms, and at least one of said R and R^1 groups being other than hydrogen;

R^3 is a carbocyclic aryl having at least 6 ring carbon atoms and independently substituted at one or more ring positions by haloalkyl, substituted or unsubstituted thioalkyl having from 1 to about 3 carbon atoms, substituted or unsubstituted alkylsulfinyl, substituted or unsubstituted alkylsulfonyl, and haloalkoxy; and pharmaceutically acceptable salts thereof; with the exclusion of N-(1-naphthyl)-N'-(3-

no halo sub ?

trifluoromethylphenyl)-N'-methylguanidine, N-(1-naphthyl)-N'-(3-trifluoromethylphenyl)-N'-ethylguanidine, N-(8-coumarinyl)-N'-(3-trifluoromethylphenyl)-N'-methylguanidine, and N-(8-coumarinyl)-N'-(3-trifluoromethylphenyl)-N'-ethylguanidine, and the proviso that R^3 is not substituted by trifluoromethyl when one of said R and R^1 groups is hydrogen and R^2 is hydrogen.

2. A compound of claim 1 of the following Formula Ia:



Ia

wherein R, R^1 and R^2 are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkoxy, substituted or unsubstituted thioalkyl, substituted or unsubstituted aminoalkyl, substituted or unsubstituted carbocyclic aryl having at least about 6 ring carbon atoms, substituted or unsubstituted aralkyl having at least about 6 carbon ring atoms, or a substituted or unsubstituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 ring members in each ring and from 1 to 3 hetero atoms, and at least one of said R and R^1 groups being other than hydrogen;

R^4 is independently substituted at one or more ring positions by haloalkyl, substituted or unsubstituted thioalkyl having from 1 to about 3 carbon atoms, substituted or unsubstituted alkylsulfinyl, substituted or unsubstituted alkylsulfonyl, and haloalkoxy; and pharmaceutically acceptable salts thereof; with the exclusion of N-(1-naphthyl)-N'-(3-trifluoromethylphenyl)-N'-methylguanidine, N-(1-naphthyl)-N'-(3-trifluoromethylphenyl)-N'-ethylguanidine, N-(8-coumarinyl)-N'-(3-trifluoromethylphenyl)-N'-methylguanidine, and N-(8-coumarinyl)-N'-(3-trifluoromethylphenyl)-N'-ethylguanidine, and the proviso that R^4 is not trifluoromethyl when one of said R and R^1 groups is hydrogen and R^2 is hydrogen.

3. A compound of claim 2 wherein R^4 is a meta substituent.

4. A compound of claim 2 wherein R^4 is substituted or unsubstituted alkylthio having 1 to 3 carbon atoms, substituted or unsubstituted alkylsulfinyl, substituted or unsubstituted alkylsulfonyl, or substituted or unsubstituted haloalkoxy.

5. A compound of claim 2 selected from the group of:
N-(1-naphthyl)-N'-(3-methylthiophenyl)-N'-methylguanidine;
N-(1-naphthyl)-N-methyl-N'-(3-methylthiophenyl)guanidine;
N-(1-naphthyl)-N,N'-dimethyl-N'-(3-methylthiophenyl)guanidine;
N-(1-naphthyl)-N'-(3-methylthiophenyl)guanidine;
N-(1-naphthyl)-N'-(3-methylsulfinylphenyl)-N'-methylguanidine;
N-(1-naphthyl)-N-methyl-N'-(3-methylsulfinylphenyl)guanidine;
N-(1-naphthyl)-N,N'-dimethyl-N'-(3-methylsulfinylphenyl)guanidine;
N-(1-naphthyl)-N'-(3-methylsulfinylphenyl)guanidine;
N-(1-naphthyl)-N'-(3-methylsulfonylphenyl)-N'-methylguanidine;
N-(1-naphthyl)-N-methyl-N'-(3-methylsulfonylphenyl)guanidine;

N-(1-naphthyl)-N,N'-dimethyl-N'-(3-methylsulfonylphenyl)guanidine;
N-(1-naphthyl)-N'-(3-methylsulfonylphenyl)guanidine;
N-(1-naphthyl)-N'-(3-trifluoromethylthiophenyl)-N'-methylguanidine;
N-(1-naphthyl)-N-methyl-N'-(3-trifluoromethylthiophenyl)guanidine;
N-(1-naphthyl)-N,N'-dimethyl-N'-(3-trifluoromethylthiophenyl)guanidine;
N-(1-naphthyl)-N'-(3-trifluoromethylthiophenyl)guanidine;
N-(1-naphthyl)-N'-(3-pentafluoroethylphenyl)-N'-methylguanidine;
N-(1-naphthyl)-N-methyl-N'-(3-pentafluoroethylphenyl)guanidine;
N-(1-naphthyl)-N,N'-dimethyl-N'-(3-pentafluoroethylphenyl)guanidine;
N-(1-naphthyl)-N'-(3-pentafluoroethylphenyl)guanidine;
N-(1-naphthyl)-N'-(3-trifluoromethoxyphenyl)-N'-methylguanidine;
N-(1-naphthyl)-N-methyl-N'-(3-trifluoromethoxyphenyl)-N'-methylguanidine;
N-(1-naphthyl)-N'-(3-trifluoromethoxyphenyl)guanidine;
N-(3-ethylphenyl)-N'-(3-methylthiophenyl)-N'-methylguanidine;
N-(3-ethylphenyl)-N,N'-dimethyl-N'-(3-methylthiophenyl)guanidine;
N-(3-ethylphenyl)-N'-(3-methylthiophenyl)guanidine;
N-(3-ethylphenyl)-N'-(3-methylsulfinylphenyl)-N'-methylguanidine;
N-(3-ethylphenyl)-N,N'-dimethyl-N'-(3-methylsulfinylphenyl)guanidine;
N-(3-ethylphenyl)-N'-(3-methylsulfinylphenyl)guanidine;
N-(3-ethylphenyl)-N'-(3-methylsulfonylphenyl)-N'-methylguanidine;
N-(3-ethylphenyl)-N,N'-dimethyl-N'-(3-methylsulfonylphenyl)guanidine;
N-(3-ethylphenyl)-N'-(3-methylsulfonylphenyl)guanidine;
N-(3-ethylphenyl)-N'-(3-trifluoromethylthiophenyl)-N'-methylguanidine;
N-(3-ethylphenyl)-N-methyl-N'-(3-trifluoromethylthiophenyl)guanidine;
N-(3-ethylphenyl)-N,N'-dimethyl-N'-(3-trifluoromethylthiophenyl) guanidine;
N-(3-ethylphenyl)-N'-(3-trifluoromethylthiophenyl)guanidine;

N-(3-ethylphenyl)-N'-(3-pentafluoroethylphenyl)-N'-methylguanidine;
N-(3-ethylphenyl)-N-methyl-N'-(3-pentafluoroethylphenyl)guanidine;
N-(3-ethylphenyl)-N-methyl-N'-(3-pentafluoroethylphenyl)-N'-methylguanidine;
N-(3-ethylphenyl)-(3-pentafluoroethylphenyl)guanidine;
N-(3-ethylphenyl)-N'-(3-trifluoromethylphenyl)-N'-methylguanidine;
N-(3-ethylphenyl)-N-methyl-N'-(3-trifluoromethoxyphenyl)guanidine;
N-(3-ethylphenyl)-N-methyl-N'-(3-trifluoromethoxyphenyl)-N'-methylguanidine;
N-(3-ethylphenyl)-N-methyl-N'-(3-trifluoromethoxyphenyl)guanidine; and
N-(3-ethylphenyl)-N'-(3-trifluoromethoxyphenyl)guanidine; and
pharmaceutically acceptable salts thereof.

6. A compound of claim 2 selected from the group of:
N-(3-methylthiophenyl)-N'-(3-methylthiophenyl)guanidine;
N-(3-methylthiophenyl)-N'-(3-methylthiophenyl)-N'-methylguanidine;
N-(3-methylthiophenyl)-N-methyl-N'-(3-methylthiophenyl)guanidine;
N-(3-methylthiophenyl)-N,N'-dimethyl-N'-(3-methylthiophenyl)guanidine;
N-(3-methylthiophenyl)-N'-(3-bromophenyl)guanidine;
N-(3-methylthiophenyl)-N'-(3-bromophenyl)-N'-methylguanidine;
N-(3-methylthiophenyl)-N-methyl-N'-(3-bromophenyl)guanidine; and
N-(3-methylthiophenyl)-N,N'-dimethyl-N'-(3-bromophenyl)guanidine;
pharmaceutically acceptable salts thereof.

7. A compound selected from the group of
N-(3-ethylphenyl)-N,N'-dimethyl(3-trifluoromethylphenyl)guanidine;
N-(3-ethylphenyl)-N-methyl-N'-(3-trifluoromethylphenyl)guanidine; N-(3-ethylphenyl)-N'-(3-trifluoromethylphenyl)-N'-methylguanidine; N-(1-naphthyl)-N'-(3-trifluoromethylphenyl)-N-methylguanidine; and N-(1-

naphthyl)-N'-(3-trifluoromethylphenyl)-N,N'-dimethylguanidine; and pharmaceutically acceptable salts thereof.

8. A method of treating a mammal suffering from nerve cell death or susceptiable to nerve cell death comprising administering to the mammal an effective amount of a compound of claims 1 or 2.

9. A method of treating a disease of the nervous system in which the pathophysiology of the disorder involves excessive excitation of nerve cells by agonists of NMDA receptors, comprising administering to a mammal exhibiting symptoms of the disease or that exhibits symptoms of the disease an effective amount of a compound of claims 1 or 2.

10. The method of claim 9 wherein said disease is selected from the group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Down's Syndrome and Korsakoff's disease, or wherein the mammal is a human suffering from epilepsy.

11. A method of inhibiting NMDA receptor-ion channel related neurotoxicity in a mammal exhibiting such neurotoxicity or susceptible thereto comprising administering to the mammal an effective NMDA receptor inhibition amount of a compounds of claims 1 or 2.

12. The method of claim 11 wherein said neurotoxicity is caused by excessive release of endogenous glutamate following the occurrence of hypoxia, hypoglycemia, brain or spinal chord ischemia, or brain or spinal chord trauma.

13. A pharmaceutical composition comprising a therapeutically effective amount of one or more compounds of claims 1 or 2 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/13245

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/15, 31/155; C07C 251/38, 279/18
US CL :514/633, 634; 564/229, 238, 239

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/633, 634; 564/229, 238, 239

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE: CA AND REGISTRY FILES

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US,A, 5,262,568 (WEBER ET AL) 16 NOVEMBER 1993, SEE ENTIRE DOCUMENT.	1-13
Y	US,A, 5,190,976 (WEBER ET AL) 02 MARCH 1993, SEE ENTIRE DOCUMENT.	1-13
Y	US,A, 4,709,094 (WEBER ET AL) 24 NOVEMBER 1987, SEE ENTIRE DOCUMENT.	1-7, 13
Y	US,A, 3,976,643 (DIAMOND ET AL) 24 AUGUST 1976, SEE COLUMNS 1-3.	1-7, 13
Y	WO,A, 91/18,868 (KEANA ET AL) 12 DECEMBER 1991, SEE PAGES 24-25.	1-7, 13
Y	EP,A, 0,179,643 (IKEDA ET AL) 30 APRIL 1986, SEE PAGES 12-14.	1-7, 13

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
01 MARCH 1995	13 MAR 1995
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer PETER O'SULLIVAN Telephone No. (703) 308-1235

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/13245

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	DE, A, 2,133,056 (GOLYSCHIN ET AL) 18 JANUARY 1973, SEE CLAIM 1 AND EXAMPLES.	1-3, 13 ---------- 1-7, 13